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McCune-Albright Syndrome with Multiple Bilateral Café au Lait Spots

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Abstract: **A 7-week-old infant developed hyperpigmented lesions at 5 days of age that gradually progressed to sharply demarcated, medium-brown macules of unusual configuration involving the neck, trunk, buttocks, upper arms, and right upper thigh. A biopsy specimen of a representative lesion showed changes of epidermal melanosis consistent with café au lait spot. At age 15 months the patient developed a limp. Roentgenographic evaluation showed widespread, bilateral changes of fibrous dysplasia, most severe in the right pelvis, femur, and tibia. At the present time he has no evidence of precocious puberty or other endocrinopathies. Despite the absence of endocrine abnormalities, these findings are consistent with a diagnosis of McCune-Albright syndrome with extensive bony and cutaneous lesions.**

The McCune-Albright syndrome in its complete form is a triad characterized by cutaneous lesions of light brown pigmentation or café au lait spots, bone lesions termed polyostotic fibrous dysplasia, and hyperfunction of the endocrine system, often manifesting as precocious puberty. The classic syndrome consists of all three abnormalities; however, the diagnosis can often be made if only two features are present because each feature has special characteristics seldom found in other disorders (1). We report the case of a child with multiple, large, bilateral café au lait patches who developed extensive bony involvement in the second year of life.

CASE REPORT

A 7-week-old Caucasian male was the only child of healthy, unrelated parents. He was born uneventfully at 41 weeks' gestation with Apgar scores of 9 and 9.5 at 1 and 5 minutes, respectively. No skin lesions were noted at birth, and he was considered to be a normal infant. At 5 days of age faint hyperpigmented lesions were noted on his trunk. These gradually became more distinct as they evolved, and progressed to involve the arms, buttocks, and thigh. During that time they also darkened somewhat in color and became very sharply demarcated. Complete physical examinations performed at 2 and 6 weeks of age were otherwise normal, but because of the peculiar nature of the pigmented patches, he was referred for evaluation. His family history was negative for pigmentary problems, bone and endocrine disorders, as well as for manifestations of neurofibromatosis.

On physical examination, the infant was alert, active, and normal in appearance. His weight was 4350 g (25th percentile), his length was 53.5 cm (10th–25th percentile), and his head circumference

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was 32.5 cm (5th percentile). Examination of the skin revealed multiple, sharply demarcated, angular, medium-brown macules of various configurations distributed in a patterned fashion over the trunk, upper arms, and right upper thigh. Some areas, mainly the nape and right buttock, had lesions of linear configuration.

At 11 months of age the patient returned for reevaluation. He had continued to grow and develop normally and was free of any medical problems. An ophthalmologic examination had disclosed no ocular abnormalities. The pigmented lesions noted earlier had darkened somewhat and had extended in a couple of areas (Fig. 1). Some of them now measured up to 7 cm in diameter, and all had distinct but irregular, feathery borders. The general physical examination was again within normal limits. At this visit a punch biopsy was obtained from a representative cutaneous lesion. The specimen showed an epidermis of normal thickness with basketweave orthokeratosis. Uneven melanin deposition was present in the lowermost portions of the epidermis and the basal cell layer (Fig. 2). There was no abnormality in the number and size of the melanocytes. A sparse, superficial, perivascular, lymphohistiocytic, inflammatory cell infiltrate was present in the dermis, which was otherwise normal.

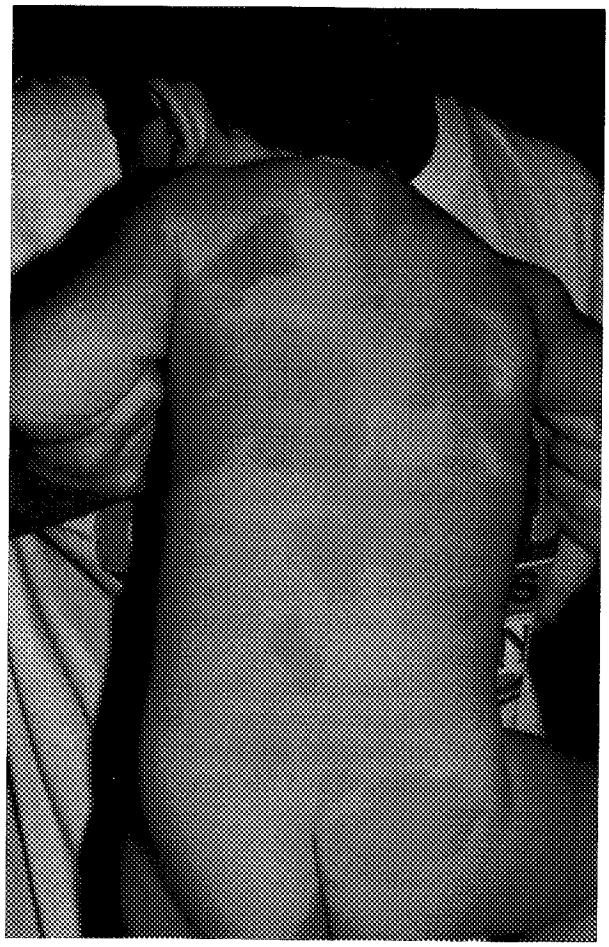

Figure 1. Sharply demarcated, angular, medium-brown macules distributed in a patterned fashion over the trunk and buttocks at 11 months of age.

At 15 months of age the child developed a limp. Radiologic evaluation showed bony lesions in several areas of the skeleton, together with a pathologic fracture in the proximal right femur. The involved long bones had lucent lesions within the metaphyses, with some cystic spaces, most obvious in the right distal femur and right proximal tibia (Fig. 3). There were also areas of involvement in the pelvis bilaterally (Fig. 4). Both proximal humeri were affected, and mild involvement of the distal radius as well as the metacarpals and phalanges was seen. The bony lesions coincided for the most part with the overlying pigmented lesions. No bone changes were noted in the skull or ribs. The sella was normal in appearance. Bone age was consistent with chronologic age. Although there were no signs of precocious puberty or other endocrine abnormalities, the combination of multiple café au lait patches and characteristic bony lesions led to a diagnosis of McCune-Albright syndrome. The patient was referred to a pediatric endocrinologist for evaluation. However, no endocrine abnormalities were found on examination, and no laboratory studies were performed.

DISCUSSION

During the early 1930s, Fuller Albright observed two women with the findings of early menarche, a bone disorder suggestive of hyperparathyroidism,

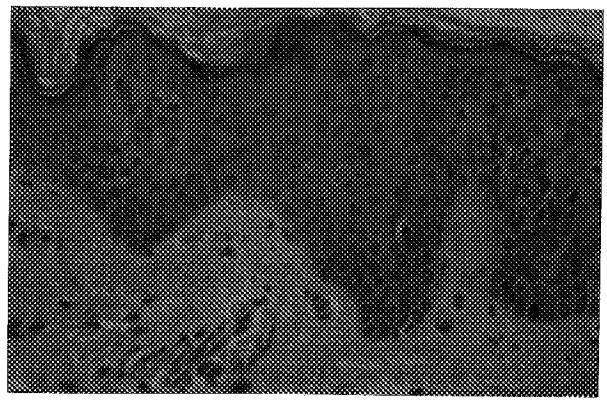

Figure 2. Skin biopsy specimen from a pigmented lesion on the left back shows uneven melanin deposition in the lowermost portions of the epidermis and the basal cell layer. (Hematoxylin & eosin; magnification 180×.)

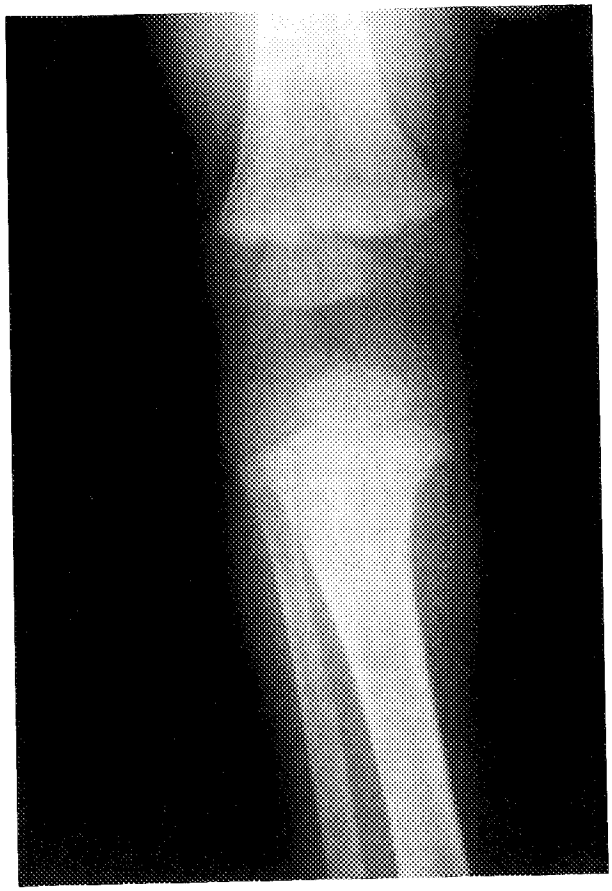

Figure 3. Radiograph at 15 months shows lucent lesions with cystic spaces involving the right distal femur and proximal tibia.

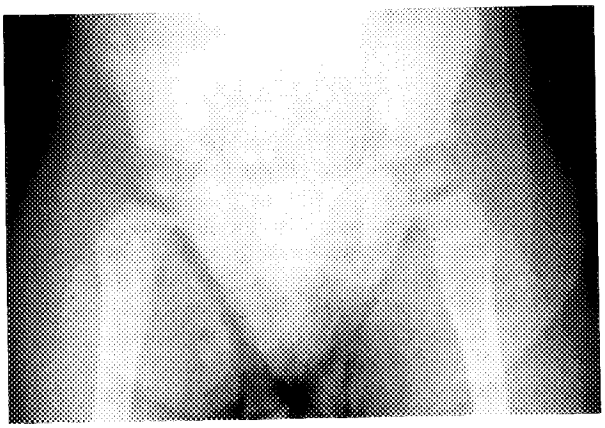

Figure 4. Radiograph of pelvis at 15 months shows similar cystlike spaces in the cortex. Lesions are most prominent in the right pelvis and femur.

and "pigmented nevi." By 1936 he was convinced that this triad of unusual findings constituted a specific syndrome, and so stated at a meeting of the Society for Pediatric Research when discussing a patient of Dr. Donovan McCune who had precocious puberty, pigmentation of the skin, and cystic bone lesions. Although the delineation of this syndrome can be attributed to Albright, McCune's published report (2) antedated that of Albright by several months (3); hence, this entity has become known as the McCune-Albright syndrome (4).

Multiple flat, pigmented lesions (café au lait) are the characteristic skin lesions of McCune-Albright syndrome (5). They can be present at birth, but are often less conspicuous than later in life (1). Alternatively, they may develop after other manifestations of the syndrome have become apparent. The macules often have irregular borders and can be arranged linearly or, less commonly, in a segmental pattern (5). They are usually confined to one side of the midline, generally the same side as the bone lesions. They may vary in size from barely perceptible patches to large areas of pigmentation, as seen in our patient (6). Sites of predilection are the head, neck, sacral area, and buttocks (1). Histologically, the pigmented macules show increased melanin deposition, mostly in the basal cell layer of the epidermis.

The characteristic bone lesions of this syndrome are termed polyostotic fibrous dysplasia. Within these lesions, normal bone is replaced by an abnormal proliferation of fibrous tissue and poorly formed bony trabeculae. On radiograms, cystlike spaces can be demonstrated in the cortex of the bone, giving it a ground glass appearance (1,5). Most commonly affected are the femurs, tibias, carpals, and tarsals, however, any bone can be involved. A significant number of patients with polyostotic bone dysplasia have craniofacial involvement. This can manifest as facial asymmetry, occipital prominence, or displacement of one or both orbits with secondary hypertelorism. The bone lesions in and of themselves are not painful; it is the complications such as pathologic fracture occurring in the areas of expansion of the cystic lesions that produce the pain. Leg length discrepancy seems to be the most frequently associated physical deformity; however, lesions of the skull may lead to facial disfigurement. Generally, the bone lesions progress in size and number until the end of the second or third decade and then become relatively stable. To date, there have been no reported cases of malignancies of the bone associated with McCune-Albright syndrome (5).

The association of multiple endocrinopathies is well established and accounts for much of the variation in the clinical spectrum of the syndrome. The original theory of primary hypothalamic dysfunc-

tion causing stimulation of the involved endocrine organs has given way to the belief that autonomous hyperfunction of the endocrine glands is responsible for the various endocrine abnormalities (4,5,7).

Sexual precocity is the most common and most carefully studied endocrine manifestation of this syndrome (1,8,9). Both this feature and the syndrome are more common in girls; the former is often manifested as menses preceding any other signs of puberty by several years (10). As many as one-third of the reported girls with this syndrome have had precocious sexual development as the initial sign (1). The small number of boys with this endocrine abnormality have had premature enlargement of the penis and testes accompanied by growth of pubic hair (1). The exact cause of the sexual precocity is unknown, however, it seems to represent hyperfunction of the end organs and occurs independent of secretion of pituitary gonadotropins. The majority of affected children develop the other manifestations of puberty at the expected age, and many of these individuals are fertile (1).

Other endocrinopathies associated with McCune-Albright syndrome include hyperthyroidism, Cushing syndrome, hypersomatotropism, hyperprolactinemia, and hyperparathyroidism. Hyperthyroidism is the second most common of these. It occurs at all ages with equal frequency in both sexes, and manifests as irritability, poor weight gain, and growth failure. The thyroid gland exhibits nodular hyperplasia, rather than the diffuse enlargement seen with lymphocytic infiltration characteristic of Graves disease. Hormone levels as well as radioiodine uptake values are elevated, and serum thyroid-stimulating hormone levels are low (11).

The various other endocrinopathies occur less frequently. Three cases of adrenal cortisol hypersecretion have been associated with McCune-Albright syndrome (12). The documented patients with associated hypersomatotropism have had the clinical features of acromegaly and excessive growth, with increased serum levels of growth hormone (1,13, 14). Three cases of hyperprolactinemia were reported in females with this syndrome. Hyperparathyroidism has also been described in three patients (1). Some of the manifestations in these individuals include hypercalcemia, renal calculi, polydipsia, polyuria, and weight loss. On surgical exploration, parathyroid hyperplasia and adenomas have been found.

Because of poor understanding of the pathogenetic mechanisms operative in this syndrome, no specific therapy is available. Management should be directed at relieving morbidity and any associated disabilities. Sun-blocking agents applied to the pigmented macules can prevent excessive tanning in these areas (1). A comprehensive orthopedic program should be instituted to prevent deformities and pathologic fractures. Bone grafting has been tried in a small number of patients in whom the bone lesions were isolated and involved limited areas. Endocrine functions must be evaluated and treated according to the individual patient. Often surgical removal of a hyperfunctioning gland is indicated; in other instances medical therapy may effectively interdict glandular hyperfunction.

The life span in most patients with McCune-Albright syndrome is normal (1,5). Associated malignancies are rare. If the bone lesions of fibrous dysplasia are extensive early in life, progression of the disease is likely to be more extensive and the prognosis poor.

McCune-Albright syndrome represents a heterogenous group of patients with cutaneous hyperpigmentation, fibrous dysplasia of bone, and a spectrum of endocrine abnormalities. Many of the reported patients have an incomplete form of the syndrome and, like our patient, lack one feature of the triad. It is important to recognize, however, that not all features develop simultaneously. Therefore all patients with café au lait patches, bone lesions suggestive of fibrous dysplasia, or unusual endocrine abnormalities should be carefully evaluated with consideration for the diagnosis of McCune-Albright syndrome.

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